

LETTER TO THE EDITOR

Reply to “Restricting maintenance allopurinol dose according to kidney function in patients with gout is inappropriate!” by Stamp et al.

We appreciate the interest shown by Professor LK Stamp et al¹ in our article concerning the appropriateness of drug prescriptions in patients with chronic kidney disease (CKD) from the prospective CKD-REIN cohort (Chronic Kidney Disease-Renal Epidemiology and Information Network).²

In the CKD-REIN cohort³ of 3033 patients, 3011 had at least one drug prescription in the 3 months immediately prior to inclusion. The objective of our study was to assess the prevalence and determinants of inappropriate drug prescription (ie, contraindicated drugs and inappropriately high doses of indicated drugs) with regard to kidney function in patients with CKD receiving nephrology care. At baseline, the median [interquartile range] number of drugs prescribed per patient was 8 [5–10]. Half of the patients had been prescribed at least one inappropriate drug. Anti-gout agents, cardiovascular drugs, and antidiabetic agents accounted for most of the inappropriate prescriptions. Indeed, more than one third of the CKD-REIN patients had been prescribed an anti-gout agent during the 3 months prior to inclusion; 51% of the allopurinol prescriptions were inappropriate with regard to the patient's kidney function and the dose level guidelines in the summary of product characteristics (SPC).

Firstly, we consider that the title of Stamp et al.'s Letter to the Editor (“Restricting maintenance allopurinol dose according to kidney function in patients with gout is inappropriate”) is itself not adapted to the current design of the CKD-REIN study. In fact, we did not have data on when allopurinol was initiated for a given patient, and so cannot determine whether patients treated by allopurinol were in the initiation phase or the maintenance phase. Furthermore, 42% of the CKD-REIN patients treated by allopurinol did not have a history of gout. Patients were considered to have a history of gout if the latter was mentioned in their medical records. A history of hyperuricaemia alone was not considered to be a history of gout. Even if hyperuricaemia was present, we could not check whether gout can never occurred or whether incident gout had been inadvertently omitted from the medical records. It should be noted that 159 of the 323 allopurinol-treated patients without a history of gout (49%) were given a dose that was too high with regard to their renal function (according to the SPC). However, the treatment of hyperuricaemia in the absence of gout appears to be common.^{4,5} Yang et al⁴ highlighted the large proportion of CKD patients treated with allopurinol for elevated uric acid despite the absence of gout

symptoms. Lastly, the treatment of hyperuricaemia without gout symptoms is not recommended.⁶

Secondly, our objective was to take a snapshot of inappropriate drug prescriptions at a given time, rather than to assess the relevance of guidelines with descriptive data alone. Our hypothesis is that prescribers may not be aware of the dose adjustments recommended in CKD patients—even though these adjustments are described in the SPCs. For allopurinol in particular, the SPC and the 2016 European League Against Rheumatism (EULAR) guidelines recommend a dose reduction with falling renal function.⁶ We wish to emphasize that regulatory agencies in many European countries require this adjustment and that the EULAR took this into account in their 2016 evidence-based guidelines.⁶

Thirdly, we agree with Stamp et al that allopurinol hypersensitivity syndrome (AHS) is a rare but very serious adverse drug reaction, with a high mortality rate.⁷ The EuroSCAR study revealed that allopurinol was the drug most commonly associated with Stevens-Johnson syndrome and toxic epidermal necrolysis.⁸ Furthermore, off-label use appeared to be a risk factor for mortality.⁹ Chaby et al⁵ showed that allopurinol was one of the drugs most frequently involved in severe cutaneous reactions (SCARs) and that off-label use accounted for more than half of the allopurinol-induced SCARs. CKD is a major risk factor for AHS and SCARs.^{9–11} Indeed, Chung et al.'s case-control study¹⁰ found that kidney failure was significantly associated with the delayed clearance of plasma oxypurinol; the latter compound might have antigenic properties and thus might stimulate cytotoxic T lymphocytes.

Fourthly, Stamp et al cited studies in which gradually increasing the dose above that based on kidney function was safe in CKD patients.^{12–15} However, most of the literature studies on this aspect have retrospective designs and small sample sizes and therefore are not high-quality evidence. Urate and oxypurinol accumulate in patients with CKD.^{16–19} In this situation, increasing the dose of allopurinol might be beneficial by controlling the high urate level. However, given that (i) the guidelines on oxypurinol dose adjustment in CKD are not particularly clear and (ii) the threshold between therapeutic and toxic doses is not well defined, high doses of oxypurinol may increase the risk of toxicity in patients with severe renal impairment. Nevertheless, assessing the safety profile of allopurinol in CKD patients is difficult, given that the incidence of allopurinol-induced SCARs is very low

(<1/1000 patient-years^{6,7}). Only very large cohorts could give reliable data on the safety of allopurinol.

In conclusion, our study of prescriptions in CKD patients highlighted that the SPC's recommendations on dose adjustment of allopurinol (amongst other drugs) according to renal function were not universally followed by prescribers. Based on all the above arguments, we believe that our present paper is not directed to explore outcomes in people with gout and CKD and we disagree with the suggestion by Professor LK Stamp et al that our article could alter outcomes in these patients.

COMPETING INTERESTS

There are no competing interests to declare.

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